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Genetic Association between Interleukin Genes and Alopecia Areata in Jordanian Patients

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ABSTRACT

Objectives: Alopecia areata (AA) is a multifactorial autoimmune disease with a strong genetic predisposition. A variety of genes involved in immunity and inflammatory responses, such as cytokines, are suspected to increase the risk of developing AA. In which, different interleukin (IL) genes that associated with several autoimmune diseases and AA in varied populations. The objective of this study was to investigate the possible genetic association of AA with ten variants of single nucleotide polymorphism (SNP) in *IL12B*, *IL13*, *IL16*, *IL17A*, and *IL18* genes among Jordanian patients. ***Methods***: In this case-control study, peripheral blood samples of 152 Jordanian AA patients and 150 controls (total of 302 subjects) were collected, genomic DNA extracted and genotyped, based on which their allele and genotype frequencies were assessed. ***Results:*** In the rs11073001 SNP located in the exon region of the *IL16* gene, the A allele was distributed more frequently in AA patients ($p = 0.01$). A difference was found between the patients and the controls for the rs17875491 SNP in the promoter region of the *IL16* gene ($p = 0.04$). The mean age of onset was 27.3±12.6 with male predominance. Most patients (68.4%) were asymptomatic but some reported experiencing associated sensations before the hair loss episodes. The patchy patterns of alopecia were the most common (90.3%). Nail changes were found in 7.3% of the patients. ***Conclusions:*** The findings support the hypothesis of the involvement of *IL16* gene in the etiology of AA. Moreover, it emphasizes the variations in the genetic component of AA, as well as the clinical phenotypes among different ethnic groups.

Alopecia areata (AA) is a common autoimmune dermatological disease that causes hair loss of variable severity in any hair-bearing area.[1,2] It presents with different sizes and patterns of nonscarring hair loss mediated by targeted, organ-specific inflammatory responses of the hair follicles.[3,4] There are several subtypes of alopecia, with patchy AA forming 90% of the cases. The remaining 10% include alopecia totalis (AT), alopecia ophiasis (AO), and alopecia universalis (AU), the last one being the severest and the most differentiated form of the disease.[2,5] The incidence of all forms of AA in the general population varies depending on the studied ethnicity. Studies have reported a prevalence range of 0.5–6.9%.[6–12] The disease can present at any age, though it is rare in infants.[13] The onset of AA has been estimated to occur in 60% of the patients before the age of 20 years, with a higher prevalence between ages 10 and 25 (70%).[14] Although the disease seems to be equally distributed in both sexes, it is still debated whether AA is more predominant in males or females, depending on the studied population.[2,5,14,15]

AA is a complex multifactorial disease with poorly understood etiology. The unpredictability of the phenotypic and genotypic variations associated with AA suggests the involvement of various environmental, immunological, epigenetic, and genetic factors.[1,2,16] Immunity and genetics are likely to be the main contributors.[17] It is evident from several studies that AA is triggered by autoimmune inflammatory processes, with cytokines as the vital players.[18] Cytokines and interleukins (ILs) are subjected to several disease-association studies due to their critical role in the pathogenesis of various autoimmune diseases using candidate gene association studies, transcriptional profiling, and large-scale genome-wide association techniques.[1,14] The genetic polymorphisms of cytokines are found to affect the transcriptional level of genes, causing

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interindividual variations and then affecting diseases outcome.[14]

Several IL genes have been selected in this study for several reasons, including *IL12B*, *IL13*, *IL16*, *IL17A*, and *IL18*, are known to be associated with different autoimmune diseases and different significant clinical variables within alopecia patients, but their genetic variations that contribute to risk for AA are not well reported in the general population.[18] In addition, these genes were selected on the basis of their known biological functions and their role in immune response.[14,18] Moreover, in order to detect single nucleotide polymorphisms (SNPs) that could be associated with AA among the Jordanian population, several SNPs within these genes (*IL12B* (rs3212227), *IL13* (rs848), *IL16* (rs17875486, rs17875491, rs11073001, rs1803275), *IL17A* (rs2275913), and *IL18* (rs187238, rs1946518, rs549908)) were selected based on previous association studies, for their position to guarantee the effects on gene expression level or based on a high degree of linkage disequilibrium (haplotype) between these SNPs. Therefore, this study aimed to determine whether these SNPs in the *IL12B*, *IL13*, *IL16*, *IL17A*, and *IL18* genes involve in susceptibility to AA in the Jordanian population using the candidate gene approach and evaluate the epidemiological characteristics related to the disease.

METHODS

This study was conducted under the provisions of the Human Ethics Standard in compliance with the Institutional Review Board (IRB) guidelines. The IRB committee at Jordan University of Science and Technology approved the conducting of this study in the Jordanian community (Ref. 13/104/2017). This granted the researchers the permission to recruit participants and collect their blood samples and clinical data. Written informed consent was obtained from participants/their parents (guardians). The subjects were N = 152 dermatology patients diagnosed with AA (107 male; 45 female) who were attending dermatology clinics at the Jordanian Royal Medical Services hospitals, and King Abdullah II University Hospital in Jordan. The control group comprised of 150 patients (129 male; 21 female) with no history of AA, randomly selected from among the Jordanians attending the same clinics for other dermatological issues.

The patients were in the age range 13–67 years (mean 31.1±12.4), while that of the control group was 17–64 years (mean 33.9±9.8). The age groups of the entire cohort of 302 participants (study and control) were classified into three bands of 18 years each (13–31; 32–50; 51–69). Assessment of the patients was conducted according to the standard evaluation guidelines for AA identification.[19] This study adopted the general characteristics for controls summarized and categorized in 2017 by AL-Eitan et al.[20]

Ten SNPs within the five candidate IL genes were selected based on their known implications in AA studies or association with other autoimmune diseases. Genomic DNA was isolated using Wizard® Genomic DNA Purification Kit (Qiagen, Germany) was provided by Al-Eitan et al,[20] upon a research collaboration. DNA samples were genotyped in duplicate with a success rate of ≥ 95% using the Sequenom MassARRAY® system (iPLEX GOLD) (Sequenom, San Diego, CA, USA), in collaboration with the Australian Genome Research Facility.

Genotyping frequencies, including examination for ascertainment bias (because there were significantly more male patients in our study) were estimated by Hardy-Weinberg equilibrium (HWE) analysis using SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and the SNPStat web tool (https://www.snpstats.net/start.htm) as well as genotypic, allelic, and haplotype association. Odds ratio (OR) with 95% CI was used, and $p < 0.05$ was considered statistically significant. Deviations from HWE were assessed by the chi-square test.

RESULTS

In this study, 152 Jordanian patients (107 male; 45 female) with AA were recruited. More than half (57.3%) of the patients were affected by AA before their thirties. There were no significant differences in terms of age or gender among the participants. The mean age of the patients when they had their first episode of AA was 27.3±12.6 (range: 13–67 years). The vast majority (90.3%) had the patchy form of alopecia, more frequently in the scalp (60.5%) and face (23.0%), with 5.3% presenting patches in both areas, and 2.3% in other body parts. The AU and AT were present in 6.6% and 3.3% patients, respectively. The nail abnormalities associated with the disorder (pitting, brittleness, striations) were seen in 7.3%

Table 1: Minor allele frequencies and their calculated Hardy–Weinberg equilibrium (HWE) *p*-values (N = 302).

Gene	SNP	MA	AA cases (n = 152)		Control (n = 150)	
			MAF	*p**(HWE)	MAF	*p**(HWE)
IL16	rs17875486	T	0.37	0.16	0.40	0.86
	rs17875491	C	0.23	0.11	0.22	0.16
	rs11073001	G	0.26	0.02	0.29	0.23
	rs1803275	A	0.05	0.31	0.06	0.46
IL18	rs187238	G	0.23	0.37	0.26	0.19
	rs1946518	T	0.41	0.62	0.43	1.00
	rs549908	G	0.24	0.51	0.25	0.27
IL12B	rs3212227	G	0.33	0.58	0.31	1.00
IL13	rs848	A	0.24	0.08	0.28	0.42
IL17	rs2275913	A	0.29	0.44	0.26	0.13

AA: Alopecia areata; MA: Minor Allele; MAF: Minor Allele Frequency; SNP: single nucleotide polymorphism.
** All p-values are correct to two decimal places.*

patients. Although 68.4% of the patients were asymptomatic, approximately one-third (31.6%) reported having associated sensations such as pruritus (severe itchy skin) and burning.

The studied variants are in HWE standards for minor allele frequency between AA patients and healthy individuals [Table 1]. Allelic association with AA susceptibility showed no association, except for the exon variant of *IL16* gene (rs11073001, $p = 0.01$), where A allele occurs more frequently among alopecia patients (74% vs. 71% in controls; Table 2). Moreover, evaluation of genotype frequency revealed the absence of any possibility to be involved in the disease development [Table 2]. Genetic association analysis using the genetic models (codominant, dominant, and recessive) revealed a significant difference between the AA patients and the controls in rs17875491 only, another *IL16* gene variant ($p = 0.04$, Table 3). Data concerning the genetic models for the other genes (*IL12B*, *IL13*, *IL17A*, and *IL18*) are not shown due to the lack of significant differences. Meanwhile, haplotype frequencies estimation of *IL16* and *IL18* variants also failed to show any association with AA in our cohort ($p > 0.05$, Table 4).

DISCUSSION

Although alopecia is often claimed to have the same incidence in both sexes,[2,9,10] our study shows a strong male predominance of 2.4:1, which indicates that males feel less stigmatized than female patients, in agreement with some previous reports.[21–24] In contrast, other studies showed a higher proportion of females,[25,26] and thus, the possibility of the effect of sex on disease frequency remains an enigma. The mean age of onset was comparable to Singapore (25.2 years)[25] and China (28.98±13.43 years),[8] but lower than in the USA (33.6 years)[9] and Taiwan (32.26±14.8 years).[27] Studies suggest that AA onset is more frequent in younger people.[10] Those in the 21–40-year age group are most likely to seek medical care than the 61–80-year age group.[25] The vast majority (90.3%) of our patients had the patchy hair loss pattern, universally the most predominant form of AA.[1,25,28,29] The scalp was involved in almost all our cases, which is the most frequently involved site in the global AA cases as well, regardless of the involvement of other body sites.[10,25,30,31] In addition, 7.3% of our patients had nail abnormalities. These are described to be more common in patients with severe forms of alopecia, the AT and the AU.[21,32] Globally, nail changes have been observed in 7–20% of AA cases, with a high prevalence as 44–66% reported in some populations.[1,32,33] Nail pitting is the most reported change.[32] Such wide variations in the prevalence of nail changes might also be attributed to being overlooked during the diagnostic procedure. Hair loss is asymptomatic in most patients[30,33] as in our subjects though some of them reported that they felt itching or burning sensations prior to an episode of hair loss.

IL12B, *IL13*, *IL16*, *IL17A*, and *IL18* genes were selected in this study because variations in

Table 2: Allelic and genotypic frequencies in control and AA patients.

Gene	SNP	Allele/genotype	AA patients n (%)	Contro n (%)	*p*-value
IL16	rs17875486	C	192 (63.2)	177 (59.8)	0.39
		T	112 (36.8)	119 (40.2)	
		CC	65 (42.8)	52 (35.1)	0.30
		CT	62 (40.8)	73 (49.3)	
		TT	25 (16.4)	23 (15.5)	
	rs17875491	G	232 (76.8)	229 (77.9)	0.87
		C	70 (23.2)	65 (22.1)	
		CC	12 (7.9)	4 (2.7)	0.06
		GC	46 (30.3)	57 (38.8)	
		GG	93 (61.2)	86 (58.5)	
	rs11073001	A	225 (74.0)	206 (70.5)	0.01
		G	79 (26.0)	86 (29.5)	
		AA	89 (58.6)	76 (52.1)	0.50
		AG	47 (30.9)	54 (37.0)	
		GG	16 (10.5)	16 (11.0)	
	rs1803275	G	287 (95.0)	277 (93.6)	0.24
		A	15 (5.0)	19 (6.4)	
		AA	1 (0.7)	1 (0.7)	0.71
		GA	13 (8.6)	17 (11.5)	
		GG	137 (90.1)	130 (87.8)	
IL18	rs187238	C	232 (76.8)	224 (74.0)	0.45
		G	70 (23.2)	78 (26.0)	
		CC	91 (59.9)	86 (57.3)	0.66
		CG	50 (32.9)	50 (33.3)	
		GG	10 (6.6)	14 (9.3)	
	rs1946518	G	178 (58.6)	167 (56.8)	0.64
		T	126 (41.4)	127 (43.2)	
		GG	50 (32.9)	47 (32.0)	0.84
		GT	78 (51.3)	73 (49.7)	
		TT	24 (15.8)	27 (18.4)	
	rs549908	T	230 (76.2)	220 (74.8)	0.21
		G	72 (23.8)	74 (25.2)	
		GG	10 (6.6)	12 (8.2)	0.88
		TG	52 (34.2)	50 (34.0)	
		TT	89 (58.6)	85 (57.8)	
IL12B	rs3212227	T	204 (67.1)	205 (69.3)	0.69
		G	100 (32.9)	91 (30.7)	
		GG	18 (11.8)	14 (9.5)	0.79
		TG	64 (42.1)	63 (42.6)	
		TT	70 (46.1)	71 (48.0)	
IL13	rs848	C	227 (75.7)	213 (72.4)	0.07
		A	73 (24.3)	81 (27.6)	
		AA	13 (8.6)	13 (8.8)	0.52
		AC	47 (30.9)	55 (37.4)	
		CC	90 (59.2)	79 (53.7)	
IL17A	rs2275913	G	215 (70.7)	219 (74.5)	0.53
		A	89 (29.3)	75 (25.5)	
		AA	15 (9.9)	13 (8.8)	
		GA	59 (38.8)	49 (33.3)	
		GG	78 (51.3)	85 (57.8)	

AA: Alopecia areata; SNP: single nucleotide polymorphism.

Table 3: Genetic haplotype frequencies estimation of IL16 and IL18 genes.

Gene	SNP	Model	Genotype	AA cases n (%)	Controls n (%)	OR (95% CI)	*p*-value
IL16	rs17875491	Codominant	G/G	93 (61.6)	86 (58.5)	1.00	0.06
			G/C	46 (30.5)	57 (38.8)	0.75 (0.46–1.21)	
			C/C	12 (8.0)	4 (2.7)	2.77 (0.86–8.93)	
		Dominant	G/G	93 (61.6)	86 (58.5)	1.00	0.59
			G/C-C/C	58 (38.4)	61 (41.5)	0.88 (0.55–1.40)	
		Recessive	G/G-G/C	139 (92)	143 (97.3)	1.00	0.04
			C/C	12 (8.0)	4 (2.7)	3.09 (0.97–9.80)	

SNP: single nucleotide polymorphism; AA: Alopecia areata; OR: odds ratio.

Table 4: Genetic model associated with AA susceptibility (Data for IL16 gene only).

Gene	Haplotype	AA cases	Control	Total	OR (95%CI)	*p*-value
IL16	TGAG	0.338	0.344	0.341	1.00	–
	CCAG	0.220	0.210	0.215	1.07 (0.68–1.66)	0.78
	CGGG	0.186	0.210	0.198	0.93 (0.59–1.46)	0.74
	CGAG	0.177	0.140	0.159	1.26 (0.78–2.05)	0.35
	CGGA	0.039	0.036	0.037	1.15 (0.47–2.82)	0.77
	TGGA	0.012	0.027	0.020	0.48 (0.13–1.77)	0.27
	TGGG	0.013	0.019	0.016	0.76 (0.17–3.42)	0.72
IL18	CGT	0.575	0.569	0.572	1.00	–
	GTG	0.226	0.253	0.239	0.90 (0.62–1.33)	0.61
	CTT	0.181	0.173	0.177	1.04 (0.67–1.62)	0.86

AA: Alopecia areata; OR: odds ratio.

the immune system and inflammation mechanism genes are considered to increase AA susceptibility[34] but are not fully elucidated. *IL12B*/rs3212227 and *IL13*/rs484 showed to lack genetic association with AA in Jordanians. *IL12B* is known to be associated with asthma[35,36] and psoriasis,[37] lack association with Crohn's disease,[38] rheumatoid arthritis,[39] and AA in patients of Central European origin,[40] and Turkey,[41] consistent with this study. Contrarily, a recent study proved the association of *IL12B* (rs3212227) polymorphism with the probability to develop AA in Iranian patients.[42] Another gene variant, *IL13*/rs484, was a susceptibility locus associated with atopic dermatitis in Europeans, Japanese, and Chinese populations.[43] Association of this polymorphism needs further investigation using other robust genetic approaches, where to the best of our knowledge, there is a dearth of reports that investigate its association with AA. Meanwhile, other regions of *IL13* were identified by genome-wide association in asthma,[44] and alopecia.[45]

Both rs17875486 and rs1803275 SNPs of the *IL16* gene showed no linkage with AA susceptibility in this study, consistent with the findings in the Korean population.[46] On the other hand, the A allele of rs11073001 and the homozygous CC genotype of rs17875491 may increase the risk for AA in Jordanian patients. Nevertheless, rs17875491 was significantly different between AA patients and controls, while rs11073001 differ between patients with and without a family history of AA.[46] Overall, these findings suggest that *IL16* gene may play a key role in AA pathogenesis. *IL17A* variant rs2275913, fail genetic association in the current report as well as in a previous study in addition to other *IL17A* variants.[47] Despite our negative findings regarding rs187238, rs1946518, and rs549908 SNPs of *IL18* gene, the latter two variants were a significant difference in Korean AA cases in comparison to the healthy controls,[47] while the former two variants were associated with AA in the Turkish population.[3] Therefore, *IL18* variants are considered major contributors to the etiopathogenesis of AA in some populations.

A limitation in this study is its small sample size. Another is the significantly low proportion of

women who were willing to participate, perhaps due to the social stigma attached to this condition.

CONCLUSION

Our findings indicate that there is a considerable association of *IL16* gene in Jordanians affected by various forms of AA. In addition, the varied genetic components among ethnicities suggest the variation in genetic association and outcomes of the disease. When comparing the Jordanians with other populations, a variation in the type of correlation, if any, can be seen between AA and different polymorphisms. In view of the dearth of studies in Jordan on genetic associations of alopecia, more studies with larger sample sizes and more equitable representation of both sexes are suggested.

Disclosure

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